12. (Amended) A method for sensitizing tumor cells to a chemotherapeutic prodrug comprising transfecting selected tumor cells with a composition comprising an isolated polynucleotide encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug, and a disease-specific responsive promoter wherein expression of the carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic prodrug.

18. (Amended) A method of inhibiting tumor growth in a patient comprising administering to a patient a composition comprising an isolated polynucleotide encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug, a disease-specific responsive promoter, wherein the dosage of said composition is one determined to produce the longest delay of recurrent disease.

REMARKS

Claims 12-14 and 18 are pending in this application. Claims 12 and 18 have been amended. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks and amendments.

I. Rejection of Claims 12-14 and 18 under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 12-14 and 18 under 35 U.S.C. §112, first paragraph, as being failing to enable one skilled in the art to which it pertains or with which it is most nearly connected to make and use the invention commensurate in scope with these claims. Specifically, the Examiner suggests that at the time of filing, the relevant art considered gene therapy as a whole to be unpredictable, as modes of delivery that would provide efficient delivery and expression of genes encoding the therapeutic protein had not been developed. The Examiner suggests that to overcome the teachings in the art the specification would need to supply direct correlative guidance as to the vector, the promoter, the expression level, the route of delivery and dosage amounts/frequency that are effective to sensitize tumor cells in a patient. Further, the Examiner suggests that the specification does not disclose any CE other than rabbit liver CE as efficient in converting APC to SN-38. Finally, the Examiner suggests that one skilled in the art would require undue experimentation in order to determine which carboxylesterase is effective in converting APC to SN-38; the route of delivery to each tumor type; and the effective amount to

sensitize tumors to the cytotoxic effect of APC. Applicants respectfully disagree.

Claim 12 has been amended as supported throughout the specification and at page 2-24, to clarify that the composition comprises an isolated polynucleotide capable of encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug. Claim 18 has been amended as supported throughout the specification and at page 17, lines 9-12, page 13, lines 25-32, page 22, line 34 through page 24, line 29, and in Examples 9 and 11.

Applicants respectfully disagree with the Examiner's assertion that undue experimentation would be required to practice the present invention. At the time of filing, prior art was available to teach a useful vector, a useful promoter, the expression level, the route of delivery and dosage amounts and frequency that are effective to sensitize human tumor cell lines. For example, attached hereto is a copy of Cavazzana-Calvo M, et al. "Gene Therapy of Human Severe Combined Immunodeficiency (SCID-1)-X1 Disease", Science 288 (5466):669-672 (2000) demonstrating the use of gene therapy. While this paper was published after our priority date, it references prior art papers demonstrating the utility of gene therapy at the time of our

original filing. Also attached hereto is a copy of Khuri FR, et al., "A Controlled Trial of Intratumoral ONYX-015, a Selective-Replicating Adenovirus in Combination with Cisplatin and 5-fluorouracil in Patients with Recurrent Head and Neck Cancer", Nature Medicine 6(8):879-885 (2000). This reference demonstrates uses of an adenovirus vector to treat selected tumors in a patient with head and neck cancer. The tumors treated with the vector were halted in their growth while the tumors treated only with chemotherapy had progressed. This paper also demonstrates the utility of gene therapy at the time of filing.

The specification discloses that CPT-11 is routinely administered or delivered to patients, but that the conversion to SN-38 is not high. Delivery of the composition of the present invention to inhibit tumor growth in a patient by injection is clearly set forth in the specification at page 28, line 9; also administration to the margins of a tumor either the time of surgery, by stereotaxic injection, or by implantation of a time-release polymer or other material is also disclosed at Example 11; further, the specification discloses at page 28, line 23 -24 that modes of administration are well known to those of skill in the art. Further, while the specification clearly teaches that rabbit liver CE and human intestinal CE are useful in

metabolizing prodrugs and inactive metabolites thereof (such as CPT-11 and APC), it is further taught that computer modeling studies indicate the ability of a carboxylesterase to activate CPT-11 is dependent on the residues that form the entrance to the active site gorge. See page 24, lines 17-19. It is also clearly disclosed that other carboxylesterases with residues similar to those forming the entrance to the active site gorge of these proteins will be useful in metabolizing prodrugs and inactive metabolites thereof. See page 24, lines 20-24. Additionally, it is respectfully pointed out that the claims of the present invention are all limited to only carboxylesterases which are capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug. Further, claim 14 limits the prodrug to CPT-11 and APC. Accordingly, the carboxylesterases capable of being used in the claim methods are easily distinguished from carboxylesterases which are not useful, using conventional methods described in the application, and specifically at page 22 line 34 through page 23, line 25 (relating to assay for the metabolism of o-NPA), page 24, lines 15-24, page 25, line 14 to page 26, line 29. Finally, as shown throughout the specification and at Example 9 and 11 the compositions of the present invention are administered to permit

determination of the most tolerated, effective schedule and dosage of the compositions to produce the longest delay of recurrent disease. The starting point for the animal experiments is injection of 10^5 to 10^8 pfu of a composition of the present invention. One skilled in the art would be able to routinely assess a patient and determine the correct dosage of the composition to be administered based upon the data disclosed in the present invention.

Withdrawal of this rejection is respectfully requested.

II. Rejection of Claims 12 under 35 U.S.C.§112, second paragraph

The Examiner has rejected claims 12-14 and 18 under 35 U.S.C. §112, second paragraph, as being indefinite. The Examiner has suggested that claim 12 omits an essential step amounting to a gap between the steps. In an effort to facilitate prosecution and clarify the invention Applicants have incorporated the claim language suggested by the Examiner into claim 12.

Withdrawal of this rejection is respectfully requested.

III. Double Patenting

The Examiner has provisionally rejected claims 12-14 and 18 under 35 U.S.C. § 101 as claiming the same invention as that of claims 11-13 and 17 of co-pending Application No. 09/622,568.

Applicants are hereby requesting that this rejection be held in abeyance since both applications are currently pending.

IV. Conclusion

Applicant believes that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made".

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

Date: **April 29, 2002**

Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515

Version with Markings to Show Changes Made

In the claims:

Claims 12 and 18 have been amended as follows:

12. (Amended) A method for sensitizing tumor cells to a chemotherapeutic prodrug comprising transfecting selected tumor cells with a composition ~~of claim 8~~ comprising an isolated polynucleotide encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug, and a disease-specific responsive promoter wherein expression of the carboxylesterase renders the tumor cells more susceptible to the cytotoxic effect of said chemotherapeutic prodrug.

18. (Amended) A method of inhibiting tumor growth in a patient comprising administering to a patient a composition ~~of claim 8~~ comprising an isolated polynucleotide encoding a carboxylesterase capable of metabolizing a chemotherapeutic prodrug and inactive metabolites thereof to active drug, a disease-specific responsive promoter, ~~and APC,~~ wherein the dosage of said composition is one determined to produce the longest delay of recurrent disease.